Article

Neurodevelopmental outcome of preterm infants with isolated grade I intraventricular hemorrhage: a matched case-control study

Jantien Dewulf [a], Luc Breysem [b], Katrien Jansen [a], Els Ortibus [a], Liesbeth Thewissen [a], Gunnar Naulaers [a]

[a] Department of Development and Regeneration, University Hospitals Leuven, Leuven, Belgium.

[b] Department of Radiology, University Hospitals Leuven, Leuven, Belgium.

jantien.dewulf@uzleuven.be

Keywords

Preterm, intraventricular hemorrhage, neurodevelopmental outcome, ultrasound

Abstract

Background: Germinal matrix and intraventricular hemorrhages remain one of the most common complications along preterm infants, detected by cranial ultrasound. Especially the impact of low-grade intraventricular hemorrhages on neurodevelopmental outcome has been the source of debate.

Objective: To determine the neurodevelopmental outcome of preterm infants (≤32 weeks) with isolated grade I intraventricular hemorrhage at 24 (19-30) month's corrected age.

Methods: A single-center matched case-control study of preterm infants born at ≤32 weeks' gestation between January 1, 2011 and December 31, 2016 and diagnosed with an isolated grade I intraventricular hemorrhage on cranial ultrasound. Cases were matched with their corresponding control (without intraventricular hemorrhage) based on gestational age (same week), birth weight (±250g), sex and year of birth (born within 2 years after birth of the corresponding case). Neurodevelopmental outcomes were compared at 24 (19-30) months' corrected age.

Results: The final study cohort consisted of 52 cases and 52 matched controls. Sixty-six point three percent of eligible survivors completed follow-up. Infants with grade I intraventricular hemorrhage had significantly lower mean psychomotor developmental index (PDI) scores and a higher rate of motor delay (PDI <85) than those without intraventricular hemorrhage. Furthermore, significantly less preterm infants with grade I intraventricular hemorrhage received antenatal corticosteroids and were inborn, while vaginal delivery occurred significantly more in the grade I intraventricular hemorrhage group.

Conclusions: At 19-30 month's corrected age, preterm infants with isolated grade I intraventricular hemorrhage had a significantly poorer motor outcome than their matched controls with normal cranial ultrasound.

Introduction

Germinal matrix and intraventricular hemorrhages (GMH-IVH) remain one of the most common complications among preterm infants with rates varying between 25% and 35% in extremely low birthweight (ELBW, birthweight < 1000g) or extremely preterm infants (<28 weeks' gestation) (1). Grading of IVH is still most frequently based on the Papile classification in which grade I IVH refers to GMH, grade II to an IVH without ventricular dilatation, grade III to an IVH with ventricular dilatation and grade IV to an IVH with parenchymal involvement (2). Nowadays grade IV IVH is less used and grade I-III with or without periventricular hemorrhagic infarction (PHI) is more accurate (3). Although survival and neurodevelopmental outcomes of preterm infants have improved in recent decades, the rate of infants at risk of developmental delay remains high, even for those born moderately preterm (4). High-grade (III-IV) IVH are known to be associated with an adverse neurodevelopmental outcome, but the impact of low-grade (I-II) IVH is more controversial (5–7). The germinal matrix is a source for proliferation of oligodendroglial precursor cells from which these subsequently migrate to the cortical layers. Here, they will differentiate and start producing myelin in the post term period (8) . The peak of migration is situated between 23 and 28 weeks' gestation (9). It is therefore suggested that even low-grade IVH have the potential to destroy these precursor cells and affect migration and myelination, especially in extremely preterm infants (6,8,10). This could result in impaired neurodevelopmental outcome. Nevertheless, several papers described different outcomes. Some studies report significant neurodevelopmental disabilities in preterm infants with low-grade IVH, while others rejected this hypothesis particularly those who utilized MRI as adjuvant neuroimaging (1,5,6,7,9,10–22). The aim of this study was to examine the impact of isolated grade I IVH on neurodevelopmental outcome at 24 (19-30) months' corrected age (CA).

Materials and Methods

Eligibility Criteria

This study was approved by the Research Ethics Committee UZ/KU Leuven, approval number [MP018241]. It is a matched case-control study on prospectively collected data of preterm infants admitted to a level III NICU at Leuven, Belgium. Preterm infants born at a gestational age of ≤ 32 weeks, between January 1, 2011 and December 31, 2016 and diagnosed with a grade I IVH on cranial ultrasound (cUS) were eligible for this study. Infants with grade II-IV IVH, other intracranial hemorrhages (lobar cerebral hemorrhages, thalamoventricular hemorrhages and cerebellar hemorrhages), focal infarction and/or cystic/non-cystic white matter disease on cUS were excluded as were infants with genetic disorders or neonatal meningitis. Cystic white matter disease was scored using the grade classification (grade II-IV) by de Vries et al (23). Non-cystic white matter disease was defined as periventricular echogenicity present for more than 7 days, isolated ventriculomegaly or irregular echodensities without ventriculomegaly. Controls without IVH were also retrieved from the neonatal database and were matched with cases based on gestational age (GA, same week), birth weight (±250g), sex and year of birth (born within 2 years after birth of the corresponding case). As 4 cases could not be matched with a corresponding control based on these criteria, these were excluded from the study.

Variables

Perinatal and neonatal characteristics were collected from the neonatal database or medical record. Perinatal data included antenatal corticosteroid use, defined as both complete (2 doses at 24-hour interval) and incomplete therapy, and chorioamnionitis/funisitis whose diagnosis was based on the anatomopathological report of the placenta. For this latter variable, both groups were slightly smaller because of the absence of a pathology report in 13 cases and 14 controls. Neonatal variables included small for gestational age (SGA, birth weight < 10th percentile), hypotension (defined as need for inotropic support), postnatal surfactant therapy (1 dose or more), necrotizing enterocolitis (NEC, defined as modified Bell stage IIA or higher), retinopathy of prematurity (ROP, defined as stage 3 or higher according to the International Classification of Retinopathy of Prematurity), patent ductus arteriosus (PDA, defined as clinical significant when medical and/or surgical treatment was necessary) and bronchopulmonary dysplasia (BPD, defined as oxygen dependence at 36 weeks' gestation (± 3 days) or at discharge, whichever came first). The presence of early (≤ 72 h) or late-onset (> 72 h) sepsis was determined using clinical characteristics and/or positive microbiology.

Imaging

IVH was diagnosed by cranial ultrasound and classified based on Papile criteria (2). This examination was performed, according to local standard procedure, on days 1, 3 (only when born at GA ≤28 weeks), 7, 14 and biweekly until term equivalent age (TEA). When abnormalities were seen, cUS was repeated weekly. In case of sepsis, NEC and postoperatively, an extra cUS was performed. Coronal and sagittal views were obtained from a transfontanellar approach. Mastoid fontanelle imaging was not routinely performed. All ultrasound images were reviewed by one neonatologist (G.N.) to exclude additional lesions. Standard MRI assessment was not performed.

Assessment of neurodevelopmental outcome

Neurodevelopmental outcomes were evaluated between 19 and 30 months' CA by a multidisciplinary team of trained psychologists, speech-language pathologists, physiotherapists and pediatricians at the Centre for Developmental Disabilities in Leuven. For assessment of neurodevelopmental outcomes, the Bayley Scales of Infant Development (BSID) and the Communicative Development Inventories, Dutch edition (N-CDI 2A) were used. The BSID second (2011-2013) and third edition (as of 2014) were used to assess motor and cognitive outcomes by the psychomotor (PDI) and mental developmental index (MDI), respectively. In this study the BSID-II PDI and MDI was chosen to work with. Therefore BSID-III scores were converted to their corresponding BSID-II scores by using a conversion table as proposed by A.F. Bos (24). To assess language development, the N-CDI 2A was used, a parent questionnaire. The mean score of PDI and MDI is 100, with a standard deviation (SD) of 15. Neurodevelopmental delay was defined as a PDI or MDI below 1 SD for the BSID-II, and language comprehension or language production < 50th percentile (p50) for the N-CDI 2A. For children who had an MDI or PDI score below 55, the score was set equal to 50 (lowest possible score on the scale) to simplify statistical analysis. A similar simplification was applied to the N-CDI 2A scores. For children with scores below the first or above the 99th percentile, the score was respectively set equal to percentile 0 and 100.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Version 28. To determine the sample size, a comparison of means was conducted. For the BSID a standard deviation of 5 was accepted. In this case a minimum of 45 patients in each group (cases and controls) was required to prove a difference of 3 points on the Bayley scale with a power of 80% and a statistical significance of 0.05. To compare categorical data, $\chi 2$ test or Fisher's exact test was used and t test was performed for continuous data. All tests were 2-sided and a p value of <0.05 was considered to be statistically significant.

Results

The complete database consisted of 776 preterm infants born at ≤32 weeks' gestation between January 1, 2011 and December 31, 2016. 24.7% of these infants developed some grade of IVH: 15.1% was diagnosed with a grade I IVH, 4.4% with a grade II IVH, 4.1% with a grade III IVH and 1.4% with a PHI. After exclusion of infants with associated abnormalities on cUS (hyperechogenic focus in the thalamic region, thalamic hemorrhage, posthemorrhagic hydrocephalus and frontal infarction), associated grade II IVH on the contralateral side, doubtful cUS findings (doubtful grade I IVH on first cUS with negative serial cUS and non-specific findings) and associated conditions (white matter disease, neonatal meningitis, genetic disorders) known to be possible contributing factors to poor neurodevelopmental outcome in preterm infants, 95 preterm infants with isolated grade I IVH were identified. Sixty-six point three percent of eligible survivors completed follow-up. Children with grade I IVH who were lost to follow-up had a significantly higher GA at birth, were less frequently intubated in the delivery room, received less frequently surfactant and systemic corticotherapy, and were less often diagnosed with BPD and ROP (shown in table 1). The final cohort consisted of 52 cases and 52 controls. A flowchart of the study enrollment is shown in Figure 1.

Baseline characteristics

Perinatal and neonatal characteristics are reported in table 2. As expected from matching, there were no significant differences in sex, birth weight or GA between groups. Significantly less preterm infants with grade I IVH received antenatal corticosteroids and were inborn, while vaginal delivery occurred significantly more in the grade I IVH group. There were no statistically significant differences in diagnoses of BPD, NEC and ROP between groups.

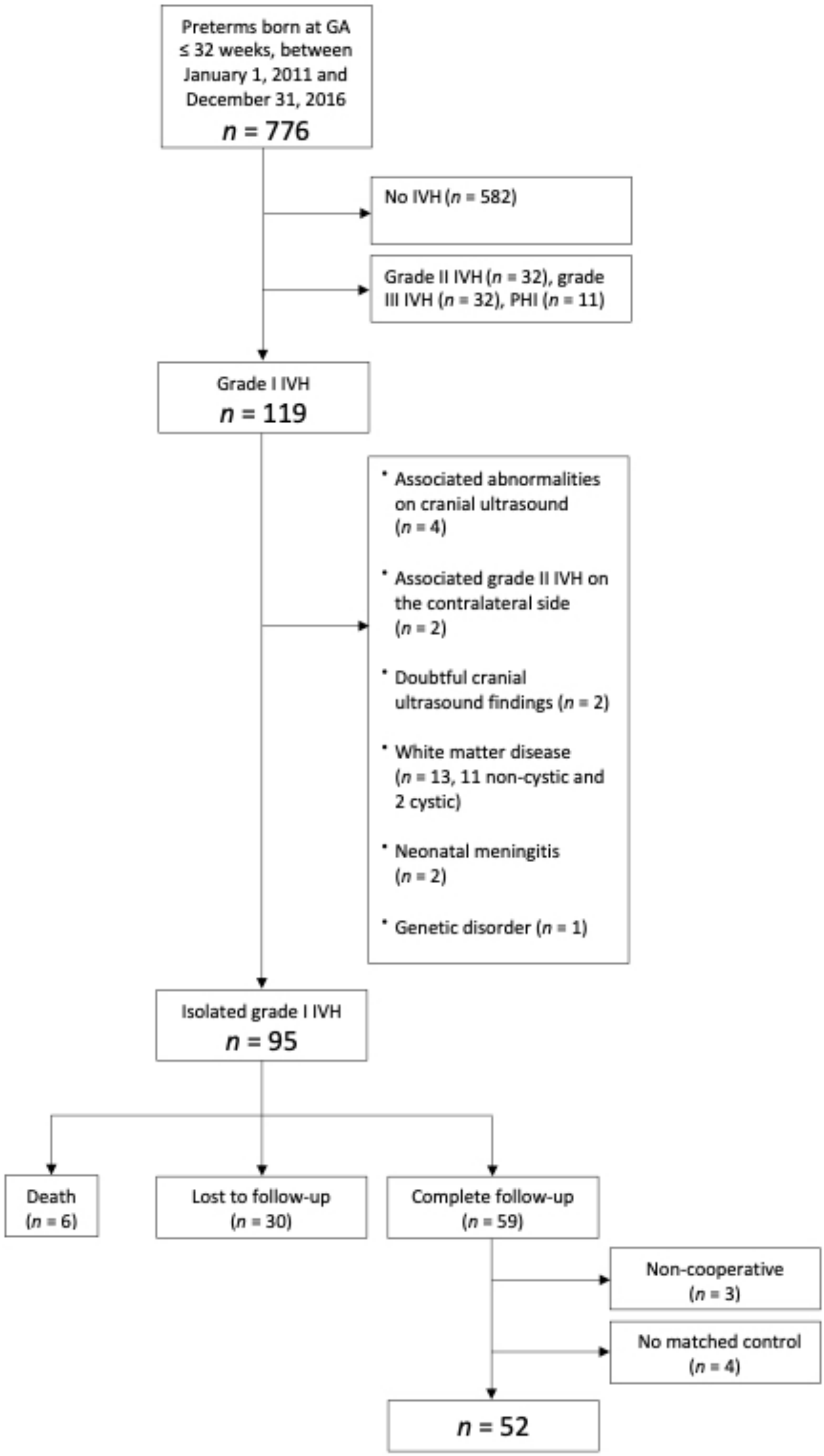
Neurodevelopmental outcomes

Infants with grade I IVH had significantly lower mean PDI scores and a higher rate of motor delay (PDI <85) than those without IVH (shown in table 3). Among these infants, two were diagnosed with cerebral palsy (CP): one with spastic diplegia, GMFCS level II and one with spastic monoplegia of the left lower limb, GMFCS level I. Among the controls with PDI below 85 there were no diagnoses of CP. Furthermore, there were no significant differences in cognitive scores between infants with and without grade I IVH. When classifying the infants according to severity of neurodevelopmental delay, there were no statistically significant differences between cases and controls (shown in table 3). Concerning language development, there were no statistically significant differences either (shown in table 4).

Discussion

This single-center matched case-control study showed that infants with grade I IVH had significantly lower mean PDI scores and a higher rate of motor delay at 19-30 months' CA than those with a normal cranial ultrasound. Furthermore, significantly less preterm infants with grade I IVH received antenatal corticosteroids and were inborn, while vaginal delivery occurred significantly more in the grade I IVH group. The findings of this research are consistent with several previous studies that reported significantly worse neurodevelopmental outcome in preterm infants with low-grade IVH (6,7,9,11–15). Bolisetty et al. and Patra et al. showed that extremely preterm and ELBW infants with low-grade IVH had increased rates of cognitive and motor

Figure 1: Flowchart of the study enrolment



impairment at 2-3 years' CA (6,12).These poor neurodevelopmental outcomes persisted up to 5 years of age, especially in the extremely preterm group, as stated by Klebermass et al. In addition, Pfahl et al. revealed that low-grade IVH in preterm infants of < 32 weeks' gestation was significantly associated with poor motor outcome at 20-24 months' CA (9,13). This was also the case in the study performed by Futagi et al. in which the rates of CP were significantly elevated in preterm infants (mean GA 28.1 weeks) with grade I IVH (7.2%) (7). Finally, in a population-based cohort study by Hollebrandse et al., it was shown that low-grade IVH in extremely preterm infants was associated with higher rates of CP, but not with intellectual ability, executive function, academic skills or overall motor function at 8 years of age (11). The results of the current study are in contrast to those of several studies that did not find any differences neither in early nor late neurodevelopmental outcomes between preterm infants with and without low-grade IVH (1,5,10,16–18,20–22). The main limitation of this study is the use of cUS without additional assessment by MRI at TEA. cUS was performed by different radiologists and there was no measure of interobserver reliability and accuracy among them. Hintz et al. reported that reliability and accuracy between 2 central readers was substantially poorer for low-grade IVH (only 26% agreement for grade I IVH) and PVL (25). The sensitivity of local reader interpretations compared with central readers for grade I IVH was 28% to 53%. Moreover, mastoid fontanelle imaging was not routinely performed. Hence, cerebellar lesions might have been missed. Previous studies reported an incidence of focal cerebellar hemorrhage (CBH) detected by cUS that increased from 3.7% in infants of ≤ 30 weeks' gestation to 9% in infants of < 32 weeks' gestation when using the mastoid fontanel window (26,27). This incidence further increased to 19% when MRI was used (27). Therefore, assessment by MRI at TEA is indispensable to detect cerebellar injury which may be associated with delayed mental and psychomotor development, and higher rates of CP as described in a meta-analysis performed by Villamor-Martinez et al. (28). On the other hand, routine neuroimaging with MRI at TEA in infants with low-grade IVH allows the recognition of additional white matter abnormalities, missed with cUS (29). GMH-IVH are in fact commonly associated with white matter injury that may impair normal development in preterm infants (19,30). Additional standardized assessment by MRI was performed in the study conducted by Reubsaet et al. in which they found that additional lesions were revealed in 54% of the infants with low-grade IVH and 38% of those with normal cUS findings (17). In 2 out of 5 infants these additional lesions could indeed explain subsequent development of CP (17). Other limitations of this study involve the retrospective design and a small sample size. However, the goal sample size of 45 infants per group was reached so that adequate power for the primary outcome could be achieved. There was also a relatively high rate of loss to follow-up (33.7%), which may have resulted in a selection bias. When comparing both groups, infants with grade I IVH who were lost to follow-up had a significantly higher GA at birth, were less frequently intubated in the delivery room, received less frequently surfactant and systemic corticotherapy, and were less often diagnosed with BPD and ROP. Another possible bias is the lack of data concerning parental socioeconomic status and age. Since these factors (especially maternal level of education and age) have a well-known influence on a child's neurodevelopmental outcome, the absence of this information may affect the results of the current study (31–33). Finally, the follow-up period up to 30 months' CA is also a limitation of this study. Behavior and/or cognitive deficits may only present beyond this age. Accordingly, Vohr et al. didn't find any differences in outcome between infants with and without low-grade IVH at 24 months of age nor at 3-5 years of age, but they did find that preterm adolescents with a history of low-grade IVH were at increased risk of neurocognitive deficits (14,31,34). The strengths of this study include the fact that cases and controls were matched so that it was possible to adjust for known risk factors for IVH such as GA, birth weight and sex. Furthermore, this research specifically looked at grade I IVH, while most studies examining the influence of IVH on neurodevelopmental outcome tend to dichotomize the 4 grades into low grades and high grades, which reduces the generalizability of the findings (1). In addition, all children with additional abnormalities on cUS or co-existing disorders that could have an IVH-independent influence on neurodevelopmental outcome were excluded.

Conclusion

This study suggests that preterm infants with isolated grade I IVH had a significantly poorer motor outcome at 19-30 months' CA than their matched controls with normal cranial ultrasound. However, these results should be interpreted with caution because of the lack of additional standardized assessment by MRI at TEA. Therefore, other abnormalities could have been missed. Although this study was sufficiently powered, the sample size was still small and a larger study replicating these analyses is recommended and could be done in the future. Finally, long-term follow-up of these infants is important to determine if these outcomes change at school age.

Conflict of interest

The authors have no conflict of interest to declare.

REFERENCES:

1. Sherlock RL, Anderson PJ, Doyle LW. Neurodevelopmental sequelae of intraventricular haemorrhage at 8 years of age in a regional cohort of ELBW/very preterm infants. Early Human Development 2005;81:909–16. https://doi.org/10.1016/j.earlhumdev.2005.07.007.
2. Papile L-A, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm. The Journal of Pediatrics 1978;92:529–34. https://doi.org/10.1016/S0022-3476(78)80282-0.
3. Ballabh P. Intraventricular Hemorrhage in Premature Infants: Mechanism of Disease. Pediatr Res 2010;67:1–8. https://doi.org/10.1203/PDR.0b013e3181c1b176.
4. Pierrat V, Marchand-Martin L, Arnaud C, Kaminski M, Resche-Rigon M, Lebeaux C, et al. Neurodevelopmental outcome at 2 years for preterm children born at 22 to 34 weeks' gestation in France in 2011: EPIPAGE-2 cohort study. BMJ 2017:j3448. https://doi.org/10.1136/bmj.j3448.
5. Radic JAE, Vincer M, McNeely PD. Outcomes of intraventricular hemorrhage and posthemorrhagic hydrocephalus in a population-based cohort of very preterm infants born to residents of Nova Scotia from 1993 to 2010. PED 2015;15:580–8. https://doi.org/10.3171/2014.11.PEDS14364.
6. Bolisetty S, Dhawan A, Abdel-Latif M, Bajuk B, Stack J, Oei J-L, et al. Intraventricular Hemorrhage and Neurodevelopmental Outcomes in Extreme Preterm Infants. Pediatrics 2014;133:55–62. https://doi.org/10.1542/peds.2013-0372.
7. Futagi Y, Toribe Y, Ogawa K, Suzuki Y. Neurodevelopmental Outcome in Children With Intraventricular Hemorrhage. Pediatric Neurology 2006;34:219–24. https://doi.org/10.1016/j.pediatrneurol.2005.08.011.
8. Volpe JJ. Impaired Neurodevelopmental Outcome After Mild Germinal Matrix-Intraventricular Hemorrhage. PEDIATRICS 2015;136:1185–7. https://doi.org/10.1542/peds.2015-3553.
9. Pfahl S, Hoehn T, Lohmeier K, Richter-Werkle R, Babor F, Schramm D, et al. Long-term neurodevelopmental outcome following low grade intraventricular hemorrhage in premature infants. Early Human Development 2018;117:62–7. https://doi.org/10.1016/j.earlhumdev.2017.12.013.
10. Payne AH. Neurodevelopmental Outcomes of Extremely Low-Gestational-Age Neonates With Low-Grade Periventricular-Intraventricular Hemorrhage. JAMA Pediatr 2013;167:451. https://doi.org/10.1001/jamapediatrics.2013.866.
11. Hollebrandse NL, Spittle AJ, Burnett AC, Anderson PJ, Roberts G, Doyle LW, et al. School-age outcomes following intraventricular haemorrhage in infants born extremely preterm. Arch Dis Child Fetal Neonatal Ed 2021;106:4–8. https://doi.org/10.1136/archdischild-2020-318989.
12. Patra K, Wilson-Costello D, Taylor HG, Mercuri-Minich N, Hack M. Grades I-II intraventricular hemorrhage in extremely low birth weight infants: Effects on

neurodevelopment. The Journal of Pediatrics 2006;149:169–73. https://doi.org/10.1016/j.jpeds.2006.04.002.

13. Klebermass-Schrehof K, Czaba C, Olischar M, Fuiko R, Waldhoer T, Rona Z, et al. Impact of low-grade intraventricular hemorrhage on long-term neurodevelopmental outcome in preterm infants. Childs Nerv Syst 2012;28:2085–92. https://doi.org/10.1007/s00381-012-1897-3.
14. Vohr BR, Allan W, Katz KH, Schneider K, Tucker R, Ment LR. Adolescents born prematurely with isolated grade 2 haemorrhage in the early 1990s face increased risks of learning challenges. Acta Paediatr 2014;103:1066–71. https://doi.org/10.1111/apa.12728.
15. Vavasseur C, Slevin M, Donoghue V, Murphy JFA. Effect of low grade intraventricular hemorrhage on developmental outcome of preterm infants. The Journal of Pediatrics 2007;151:e6. https://doi.org/10.1016/j.jpeds.2007.03.051.
16. Ann Wy P, Rettiganti M, Li J, Yap V, Barrett K, Whiteside-Mansell L, et al. Impact of intraventricular hemorrhage on cognitive and behavioral outcomes at 18 years of age in low birth weight preterm infants. J Perinatol 2015;35:511–5. https://doi.org/10.1038/jp.2014.244.
17. Reubsaet P, Brouwer AJ, van Haastert IC, Brouwer MJ, Koopman C, Groenendaal F, et al. The Impact of Low-Grade Germinal Matrix-Intraventricular Hemorrhage on Neurodevelopmental Outcome of Very Preterm Infants. Neonatology 2017;112:203–10. https://doi.org/10.1159/000472246.
18. Scott TE, Aboudi D, Kase JS. Low-Grade Intraventricular Hemorrhage and Neurodevelopmental Outcomes at 24-42 Months of Age. J Child Neurol 2020;35:578–84. https://doi.org/10.1177/0883073820922638.
19. Atef A. Impact of Low Grade Periventricular-Intraventricular Hemorrhage on Neurodevelopmental Outcome of Preterm Infants. Int J Pediatr Res 2020;6. https://doi.org/10.23937/2469-5769/1510060.
20. Beaino G, Khoshnood B, Kaminski M, Marret S, Pierrat V, Vieux R, et al. Predictors of the risk of cognitive deficiency in very preterm infants: the EPIPAGE prospective cohort: Predictors of cognitive deficiency in very preterm infants. Acta Paediatrica 2011;100:370–8. https://doi.org/10.1111/j.1651-2227.2010.02064.x.
21. Ross G, Boatright S, Auld PAM, Nass R. Specific Cognitive Abilities in 2-Year-Old Children with Subependymal and Mild Intraventricular Hemorrhage. Brain and Cognition 1996;32:1–13. https://doi.org/10.1006/brcg.1996.0054.
22. Legge N, Lutz T, Wocadlo C, Rieger I. Long-term neurodevelopmental outcome in preterm infants with intraventricular haemorrhage. J Paediatr Child Health 2022;58:1797–802. https://doi.org/10.1111/jpc.16108.
23. de Vries LS, Eken P, Dubowitz LMS. The spectrum of leukomalacia using cranial ultrasound. Behavioural Brain Research 1992;49:1–6. https://doi.org/10.1016/S0166-4328(05)80189-5.
24. Bos AF. Bayley-II or Bayley-III: what do the scores tell us? Dev Med Child Neurol 2013;55:978–9. https://doi.org/10.1111/dmcn.12234.
25. Hintz SR, Slovis T, Bulas D, Van Meurs KP, Perritt R, Stevenson DK, et al. Interobserver Reliability and Accuracy of Cranial Ultrasound Scanning Interpretation in Premature Infants. The Journal of Pediatrics 2007;150:592-596.e5. https://doi.org/10.1016/j.jpeds.2007.02.012.
26. Sehgal A, El-Naggar W, Glanc P, Asztalos E. Risk factors and ultrasonographic profile of posterior fossa haemorrhages in preterm infants. Journal of Paediatrics and Child Health 2009;45:215–8. https://doi.org/10.1111/j.1440-1754.2008.01456.x.
27. Steggerda SJ, Leijser LM, Wiggers-de Bruïne FT, van der Grond J, Walther FJ, van Wezel-Meijler G. Cerebellar injury in preterm infants: incidence and findings on US and MR images. Radiology 2009;252:190–9. https://doi.org/10.1148/radiol.2521081525.
28. Villamor-Martinez E, Fumagalli M, Alomar YI, Passera S, Cavallaro G, Mosca F, et al. Cerebellar Hemorrhage in Preterm Infants: A Meta-Analysis on Risk Factors and Neurodevelopmental Outcome. Front Physiol 2019;10:800. https://doi.org/10.3389/fphys.2019.00800.
29. Briana DD, Malamitsi-Puchner A. Low-grade intraventricular hemorrhage of preterm infants: neurodevelopmental and motor outcome. The Journal of Maternal-Fetal & Neonatal Medicine 2021;34:646–52. https://doi.org/10.1080/14767058.2019.1610741.
30. Leijser LM, de Vries LS. Preterm brain injury: Germinal matrix-intraventricular hemorrhage and post-hemorrhagic ventricular dilatation. Handb Clin Neurol 2019;162:173–99. https://doi.org/10.1016/B978-0-444-64029-1.00008-4.
31. Vohr B, Garcia Coll C, Flanagan P, Oh W. Effects of intraventricular hemorrhage and socioeconomic status on perceptual, cognitive, and neurologic status of low birth weight infants at 5 years of age. J Pediatr 1992;121:280–5. https://doi.org/10.1016/s0022-3476(05)81204-1.
32. Benavente-Fernández I, Synnes A, Grunau RE, Chau V, Ramraj C, Glass T, et al. Association of Socioeconomic Status and Brain Injury With Neurodevelopmental Outcomes of Very Preterm Children. JAMA Netw Open 2019;2:e192914. https://doi.org/10.1001/jamanetworkopen.2019.2914.
33. Veldkamp S a. M, Zondervan-Zwijnenburg M a. J, van Bergen E, Barzeva SA, Tamayo-Martinez N, Becht AI, et al. Parental Age in Relation to Offspring's Neurodevelopment. J Clin Child Adolesc Psychol 2021;50:632–44. https://doi.org/10.1080/15374416.2020.1756298.
34. Vohr BR, Garcia-Coll C, Mayfield S, Brann B, Shaul P, Oh W. Neurologic and developmental status related to the evolution of visual-motor abnormalities from birth to 2 years of age in preterm infants with intraventricular hemorrhage. J Pediatr 1989;115:296–302. https://doi.org/10.1016/s0022-3476(89)80089-7.

Table 1: Perinatal and neonatal characteristics of preterm infants with grade 1 IVH with and without assessment at 19-30 months' corrected age

Total (n = 89)	Followed-up (n = 59)	Lost to follow-up (n = 30)	p value[†]
Perinatal characteristics			
Multiple gestation	19 (32.2%)	11 (36.7%)	0.67
Antenatal corticosteroids	51 (86.4%)	25 (83.3%)	0.76[‡]
Inborn	38 (64.4%)	21 (70.0%)	0.60
Delivery			
Vaginal delivery	29 (49.2%)	14 (46.7%)	0.82
Caesarean section	30 (50.8%)	16 (53.3%)	0.82
Apgar score			
1 minute (SD)	6 (2.4)	6 (2.6)	0.91[#]
5 minutes (SD)	8 (1.6)	8 (1.5)	0.30[#]
Chorioamnionitis/funisitis (n = 75)	(n = 46) 16 (34.8%)	(n = 29) 6 (20.7%)	0.19
Neonatal characteristics			
Male	30 (50.8%)	14 (46.7%)	0.71
GA at birth, weeks, mean (SD)	28.8 (2.3)	29.8 (1.7)	0.018[#*]
Birth weight, g, mean (SD)	1214 (384)	1317 (374)	0.23[#]
SGA	6 (10.2%)	3 (10.0%)	1.00[‡]
Delivery room intubation	25 (42.4%)	6 (20.0%)	0.036[*]
Mechanical ventilation, days, mean (SD)	6 (10.5)	3 (7.4)	0.058[#]
Hypotension – inotropics	6 (10.2%)	0 (0.0%)	0.093[‡]
Surfactant	34 (57.6%)	10 (33.3%)	0.030[*]
Systemic corticotherapy	14 (23.7%)	1 (3.3%)	0.015[*]
PDA	18 (30.5%)	6 (20.0%)	0.29
BPD	25 (42.4%)	6 (20.0%)	0.036[*]
NEC	3 (5.1%)	3 (10.0%)	0.40[‡]
ROP	13 (22.0%)	1 (3.3%)	0.029[‡*]
Neonatal sepsis			
Early-onset	10 (16.9%)	6 (20.0%)	0.72
Late-onset	21 (35.6%)	7 (23.3%)	0.24
Bilateral IVH	21 (35.6%)	12 (40.0%)	0.68
Grade I IVH with BPD, NEC and/or ROP	29 (49.2%)	9 (30.0%)	0.084

† From $\chi 2$ test unless otherwise stated
‡ From Fisher's exact test
 # From independent-samples t test
** Statistically significant differences ($p<0.05$)*
GA: gestational age; SGA: small for gestational age; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; IVH: intraventricular hemorrhage

Table 2: Perinatal and neonatal characteristics

Total (n = 104)	No IVH (n = 52)	Grade I IVH (n = 52)	p value†
Perinatal characteristics			
Multiple gestation	24 (46.2%)	18 (34.6%)	0.23
Antenatal corticosteroid use	50 (96.2%)	44 (84.6%)	0.046*
Inborn	51 (98.1%)	31 (59.6%)	<0.001*
Delivery			
Vaginal delivery	10 (19.2%)	25 (48.1%)	0.002*
Caesarean section	42 (80.8%)	27 (51.9%)	0.002*
Apgar score			
1 minute (SD)	7 (2.1)	6 (2.4)	0.76#
5 minutes (SD)	8 (1.3)	8 (1.6)	0.51#
Chorioamnionitis/funisitis (n = 77)	(n = 38) 10 (26.3%)	(n = 39) 12 (30.8%)	0.67
Neonatal characteristics			
Male	26 (50.0%)	26 (50.0%)	1.00
GA at birth, weeks, mean (SD)	29.3 (2.0)	29.2 (2.1)	0.79#
GA < 28 weeks	14 (26.9%)	14 (26.9%)	1.00
Birth weight, g, mean (SD)	1262 (320)	1281 (353)	0.78#
SGA	4 (7.7%)	4 (7.7%)	1.00‡
Delivery room intubation	14 (26.9%)	20 (38.5%)	0.21
Mechanical ventilation, days, mean (SD)	4 (7.8)	5 (9.6)	0.37#
Hypotension – inotropics	1 (1.9%)	5 (9.6%)	0.21‡
Surfactant	30 (57.7%)	27 (51.9%)	0.55
Systemic corticotherapy	6 (11.5%)	11 (21.2%)	0.19
PDA	13 (25.0%)	13 (25.0%)	1.00
BPD	16 (30.8%)	19 (36.5%)	0.53
NEC	4 (7.7%)	2 (3.8%)	0.68‡
ROP	6 (11.5%)	9 (17.3%)	0.40
Neonatal sepsis			
Early-onset	5 (9.6%)	7 (13.5%)	0.54
Late-onset	13 (25.0%)	16 (30.8%)	0.51
Bilateral IVH	-	19 (36.5%)	-

† From χ2 test unless otherwise stated
‡ From Fisher's exact test
 # From independent-samples t test
** Statistically significant differences (p<0.05)*
IVH: intraventricular hemorrhage; GA: gestational age; SGA: small for gestational age; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity

Table 3: Cognitive and motor outcomes between 19 and 30 months' corrected age

Total (n = 104)	No IVH (n = 52)	Grade I IVH (n = 52)	p value†
BSID-II			
MDI < 85	20 (38.5%)	25 (48.1%)	0.32
MDI, mean (SD)	89 (20)	88 (22)	0.86#
PDI < 85	7 (13.5%)	16 (30.8%)	0.033*
PDI, mean (SD)	104 (18)	91 (21)	0.001#*
Mild developmental delay			
MDI 70-84	9 (17.3%)	16 (30.8%)	0.11
PDI 70-84	6 (11.5%)	9 (17.3%)	0.40
Moderate developmental delay			
MDI 55-69	8 (15.4%)	6 (11.5%)	0.57
PDI 55-69	1 (1.9%)	3 (5.8%)	0.62‡
Severe developmental delay			
MDI < 55	3 (5.8%)	3 (5.8%)	1.00‡
PDI < 55	0 (0.0%)	4 (7.7%)	0.12‡

† From χ2 test unless otherwise stated
‡ From Fisher's exact test
 # From independent-samples t test
** Statistically significant differences (p<0.05)*
IVH: intraventricular hemorrhage; BSID-II: Bayley Scales of Infant Development second edition; MDI: mental developmental index; PDI: psychomotor developmental; SD: standard deviation

Table 4: Language development between 19 and 30 months' corrected age

Total (n = 74)	No IVH (n = 37)	Grade I IVH (n = 37)	p value†
N-CDI 2A			
Language comprehension < p50	25 (67.6%)	23 (62.2%)	0.63
Language comprehension, mean percentile (SD)	p38 (34)	p43 (33)	0.53#
Language production < p50	27 (73.0%)	26 (70.3%)	0.80
Language production, mean percentile (SD)	p28 (31)	p33 (31)	0.48#

† From χ2 test unless otherwise stated
 # From independent-samples t test
IVH: intraventricular hemorrhage; N-CDI 2A: Communicative Development Inventories, Dutch edition; SD: standard deviation